

Model-informed comparison of the clinical relevance of four renal function markers on meropenem target attainment in critically ill septic patients

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Introduction

- Meropenem is a carbapenem antibiotic intravenously administered to critically ill septic patients.
- A poor probability of pharmacokinetic-pharmacodynamic (PKPD) target attainment (TA) was reported at the EUCAST MIC for Enterobacterales of 2 mg/L under the standard dosing (1,000 mg over 30 minutes every 8 hours) [1-2].

Objective

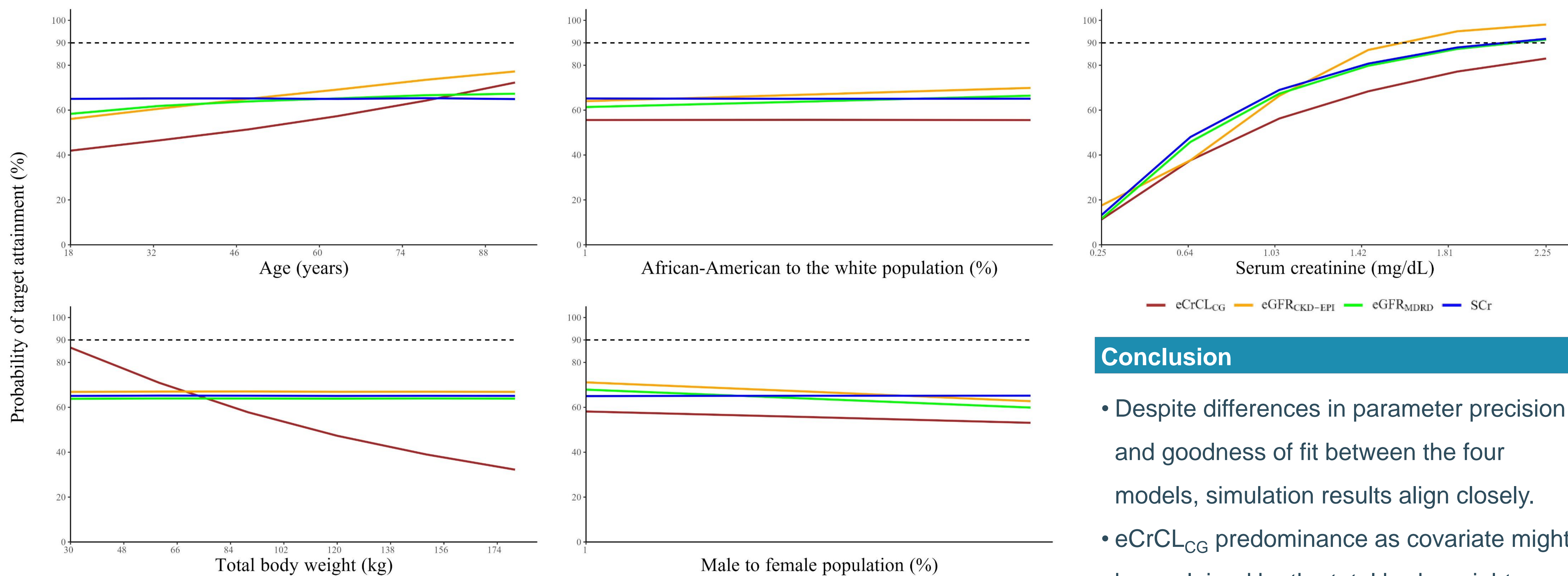
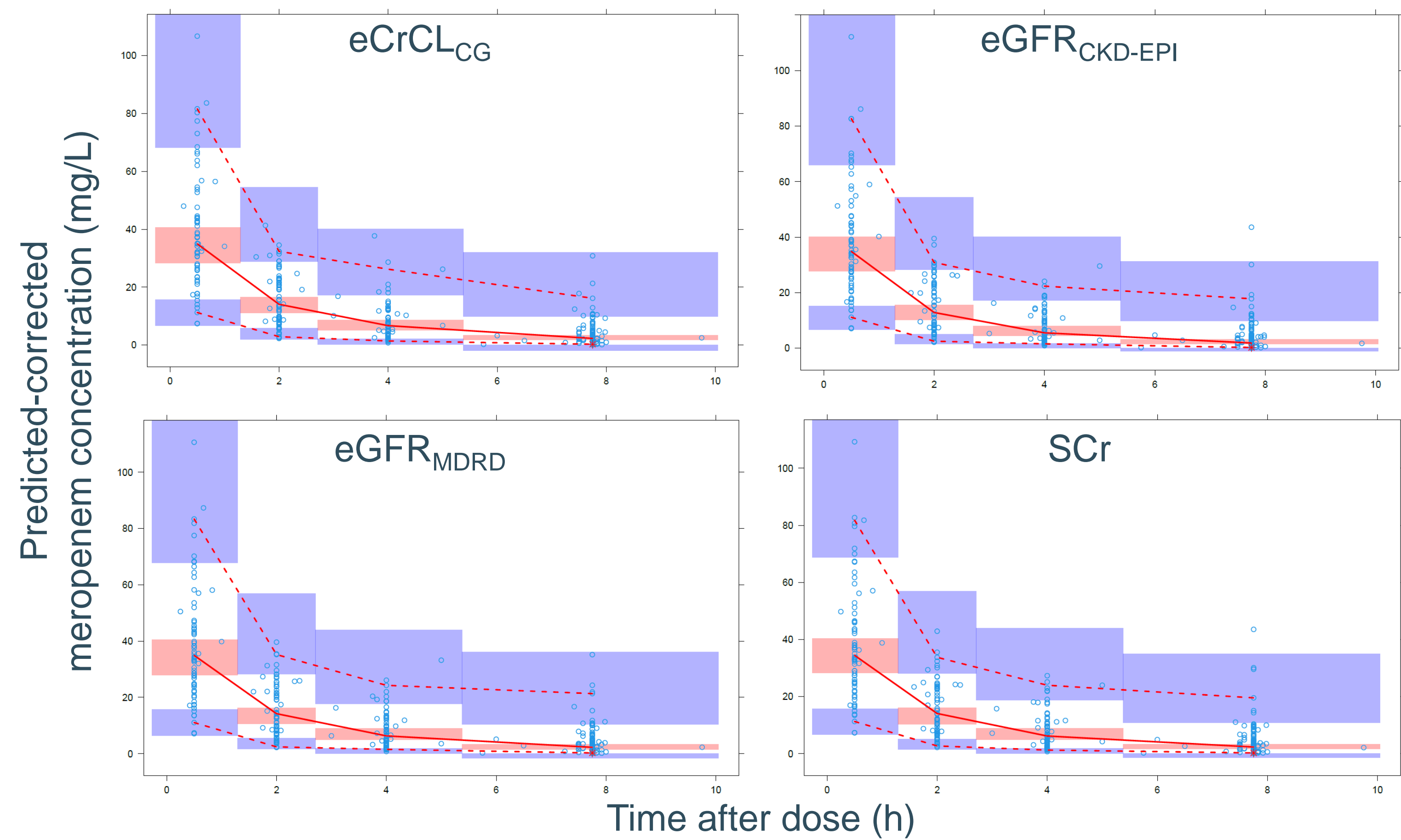
- Comparison of the clinical relevance of the impact of four kidney function markers on the clearance and TA of meropenem.

Method

- Using a real-world clinical dataset (n=58 patients; 345 meropenem concentrations), 4 popPK models were developed, each having a kidney function marker on the clearance:
 - Estimated creatinine clearance using the Cockcroft-Gault equation (eCrCL_{CG}),
 - Estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR_{CKD-EPI}),
 - Estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation (eGFR_{MDRD}),
 - Serum creatinine (SCr).
- A virtual patient was created from which the eCrCL_{CG}, eGFR_{CKD-EPI} and eGFR_{MDRD} were calculated for each virtual patient.
- Stochastic simulations (n=1,000) were performed for each virtual patient using each of the 4 popPK models under the standard dose.
 - The PKPD target was defined as unbound concentration throughout a dosing interval >2 mg/L based on 100% fT>MIC [2].
 - A probability of PKPD TA ≥90% was considered clinically relevant [3].

Results

Parameter estimate (%RSE)	No covariate	eCrCL _{CG}	eGFR _{CKD-EPI}	eGFR _{MDRD}	SCr
dOFV	—	34.38	22.93	24.25	21.18
Condition number	—	98.26	71.45	126.9	93.59
Typical values					
CL (L/h)	14.20 (8.4)	13.70 (8.4)	14.70 (8.8)	14.10 (7.6)	13.80 (8.3)
Kidney function on CL	—	0.638 (20.7)	0.950 (33.4)	0.505 (24.0)	-0.572 (27.6)
V _c (L)	21.0 (18.3)	25.50 (9.1)	25.10 (35.9)	25.00 (6.4)	24.90 (7.8)
Q (L/h)	12.9 (34.4)	8.13 (26.4)	8.89 (160.9)	8.68 (27.1)	8.68 (34.3)
V _p (L)	15.9 (21.6)	12.40 (9.8)	12.90 (119.4)	12.90 (15.4)	12.90 (19.4)
Interindividual variability					
IIV on CL (%CV)	70.8 (16.6)	57.80 (12.3)	63.20 (11.2)	64.10 (10.5)	65.50 (10.3)
IIV on V _c (%CV)	45.9 (44.3)	57.00 (16.7)	56.30 (21.1)	55.90 (16.6)	55.70 (16.7)
IIV on V _p (%CV)	80.5 (20.6)	74.40 (24.1)	77.70 (28.4)	80.00 (21.1)	80.50 (20.5)
Correlation CL and V _c (%)	95	65	67	70	69
Residual variability					
Proportional (%CV)	34.6 (22.3)	31.10 (17.3)	31.20 (19.1)	30.90 (16.5)	30.80 (16.9)
Additive (mg/L)	0.137 (57.8)	0.147 (45.6)	0.141 (49.3)	0.156 (40.1)	0.160 (40.6)



Conclusion

- Despite differences in parameter precision and goodness of fit between the four models, simulation results align closely.
- eCrCL_{CG} predominance as covariate might be explained by the total body weight.

